

## REMARKS

Claims 1-34 are pending in the application. Applicant notes with appreciation that the Examiner has indicated the allowability of claims 5, 7, and 24-32 in the Final Office Action mailed August 13, 2001 (paper no. 11). Applicant also notes that the 35 U.S.C. § 103 rejection based upon the 1996 Ingemansson rejection was withdrawn in the Advisory Action mailed January 16, 2002 (see paper 16). Applicant provides the following comments for the Examiner's further consideration.

### *Information Disclosure Statement*

Applicant notes that the Examiner has not considered the recently filed Information Disclosure Statement because a proper fee was not forwarded with the application (the Information Disclosure Statement was filed after the Final Office Action). This issue was discussed during a telephone conversation with the Examiner, wherein the Examiner indicated that the Information Disclosure Statement would be considered upon payment of the requisite fee. Therefore, Applicant has enclosed a check covering the requisite fee and requests that the Examiner consider the recently filed Information Disclosure Statement.

### *Claim Rejections – 35 U.S.C. § 103*

Claims 1 and 6 are rejected as obvious based upon Ingemansson [AT] modified by Nozick [AU] and Pinsky [AQ] or Naka [AT]. Applicant respectfully traverses this rejection and requests that it be withdrawn.

As noted in the Office Action, the Ingemansson article fails to disclose the use of calcium and nitroglycerin in a preservation solution. The Office Action sets forth that it would be obvious to modify the Ingemansson solution with the teachings of Nozick (irrigation solution having calcium) and Pinsky (preservation solution with nitroglycerin) or Naka (preservation solution with nitroglycerin). The Office Action sets forth that one of skill in the art would have been motivated at the time of the invention to make these additions in order to obtain the resulting composition as suggested by the references with a reasonable expectation of success.

Contrary to the stated reasons for the rejection, Applicant respectfully asserts that the cited prior art references fail to suggest or motivate one skilled in the art to modify the Ingemansson solution. Ingemansson does not make reference to nitroglycerin and specifically states that the preservation solution contains zero calcium. (see Table 1. Composition of Preservation Solutions). Ingemansson teaches that this solution, which completely lacks calcium, confers benefits upon vascular smooth muscle function after 24 hours of preservation.

Applicant submits that it is unlikely that a person skilled in the art would be motivated to modify Ingemansson by including calcium and nitroglycerin as proposed in the Office Action. As noted in the specification, Nozick teaches the use of calcium in an irrigation solution (not a preservation solution). Furthermore, Applicant notes that Starzl attempted to use a preservation solution containing calcium, which resulted in poor storage times. Starzl was not able to keep canine livers alive longer than 2 hours (see Applicant's specification page 13). Furthermore, neither the cited prior art nor the studies disclosed by the Applicant teach or suggest that nitroglycerin and calcium could

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be utilized together in a preservation solution, let alone the preservation solution detailed by Ingemansson in the 1995 article.

Without some hint or suggestion in the cited prior art references to perform the proposed modification, a proper *prima facie* case of obviousness can not be established. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). It is not sufficient to merely state that the proposed modification would be obvious to one skilled in the art. There must be a specific hint or suggestion in a particular reference to support combination of the references. *In re Lee*, 61 USPQ2d 1430 (Jan. 18, 2002).

None of the cited references (Ingemansson (1995), Nozick, and Pinsky) describe the unique combination of nitroglycerin, calcium and a colloidally active substance in a genuine preservation solution for organs and tissues or parts thereof (e.g. blood vessels) for transplantation. As stated in general terms in the specification, and as specifically shown in the experimental results (Figs 1 and 2), nitroglycerin and calcium have a surprising positive combinatory and previously unknown synergetic effect on organs to be transplanted, preserving their structure and function in a better way that has been known so far.

When preserving e.g. a blood vessel, it is of great importance to retain as many biological functions as possible, inter alia, both the relaxation and the contraction activity. In blood vessels there are normally two types of relaxation, i.e. endothelial derived relaxation and relaxation directly of the vascular smooth muscles. In the preservation solution according to the present invention, the action of nitroglycerin

relaxes the smooth muscles, while at the same time the presence of calcium under influence of the nitroglycerin maintains the cell membrane integrity when it is cooled. When a blood vessel is cooled down to 4° C, which is the storage temperature used in organ preservation, the endothelium get rigid due to its high content of phospholipids. At the same time the vascular smooth muscle will contract (cold induced contraction). The endothelium will then crack due to its rigidity. Nitroglycerin, which is a potent vasodilator, will prevent this cold induced spasm cracking the endothelium (calcium has no vasodilatory properties). Consequently, both types of vascular relaxation can be maintained intact. This synergistic effect is very important for the subsequent function of the transplanted blood vessel and is also much more pronounced than the corresponding effect obtained by use of either nitroglycerin or calcium separately.

The advantages of the presence of calcium in the preservation solution according to the present invention are explained in detail on description pages 6 and 7. The present inventors have found that calcium has a unique vessel endothel preserving effect, which is not previously known. They have shown that the integrity of the calcium containing glycocalax layer of the cell membranes is destroyed in preservation solutions lacking calcium (the permeability of the cell membrane is destroyed). The new effect of calcium found by the inventors in combination with the advantageous effects of nitroglycerin has led to the preservation solution according to the present invention, which to a great extent reduces the previous and well-known problem with unsatisfactory preservation of the integrity of organs, particularly blood vessel endothel.

It is also of great importance to distinguish between genuine preservation solutions and irrigation solutions. As the one skilled in the art recognizes, one of today's

requirements made on a genuine organ preservation solution is that it has to provide a substrate for metabolism. Further, it has to be hyperosmolar, thereby preventing cell oedema when lowering the organ temperature. It should also contain big molecules which gives the solution a colloidosmotice pressure, thereby making it possible to perfuse organ without creation of tissue oedema. As discussed above, the Nozick article is directed to an irrigation solution. This difference is relevant because when another researcher Starzl attempted to utilized calcium in a preservation solution the organ was only preserved for 2 hours. As such, a person skilled in the art would not expect a reasonable chance of success or even be motivated to add calcium to a preservation solution based upon the aforementioned results.

A person skilled in the art aiming to solve the problem behind the present invention would definitely not consider combining the cited prior art references as proposed in the Office Action.

### *New Claims*

Applicant submits that the new claims contain allowable subject matter. The prior art fails to disclose that the storing step would last more than 36 hours.

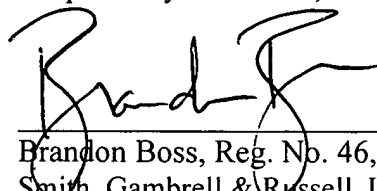
## CONCLUSION

Applicant respectfully requests allowance of the application. If any additional fees are due in connection with the filing of this response, such as fees under 37 C.F.R. §§ 1.16 or 1.17, please charge the fees to Deposit Account No. 02-4300. Any overpayment can be credited to Deposit Account No. 02-4300.

Respectfully submitted,

Date: April 15, 2002

Signature:



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\* Practice is limited to matters and proceeding before federal courts and agencies.